REMARKS

Claim Status

Claims 1-45 are pending in the present Application. Claims 13-15 and 24-45 are withdrawn from consideration. Claims 1-12 and 16-23 are rejected. Claim 1 has been amended. Support for the amendments is found at original Claims 2, 4, 9 and 10. Claims 2, 4, 9, and 10 have been canceled. No new matter has been added. Thus, entry and consideration of the amendments is respectfully requested.

REJECTIONS

Rejection Under 35 USC § 112, 2nd Paragraph

Claims 1-12 and 16-23 are rejected under 35 USC § 112, 2nd Paragraph as being indefinite.

Claim 1

The Examiner alleges that Claim 1 (and Claims 2-12 and 16-21) recites an incomplete method claim because the claim recites measurements in a biological sample, but that the method taught in the working example omits allegedly essential steps. The Examiner asserts that the alleged omitted steps include isolating PBMC's, stimulating the PBMC's in an *in vitro* culture sytem and measurement of cytokines isolated from the culture system. Thus, the Examiner asserts that the cytokines are not measured "in a biological sample". Therefore, the Examiner asserts that the claimed method is not the method disclosed in the specification, and it is unclear what the claim is directed to. Dependent Claims 2-12 and 16-21 are similarly rejected as dependent on Claim 1.

The Applicants respectfully traverse the rejection. The Applicants assert that the method as recited in Claim 1 as amended is consistent with the method described in the specification and is not indefinite. The *in vivo* aspect of the method is that patients are actually fed a potential treatment (i.e. a probiotic). Claim 1 as amended recites *inter alia* measuring the level of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine in a supernatant from cells cultured from a biological sample from a mammalian subject. The PBMCs harvested from the blood are cultured but they are not

required to be further stimulated in the method as described in the specification. See page 14, lines 17-20.

Note the contrast with the *in vitro* method in which the cells used in the *in vitro* method are taken from subjects not treated with any potential treatment. The *in vitro* method does not use a sample from a treated subject. Rather, treatment of the cells in the *in vitro* method is only done after harvesting and culturing, whereas with the *in vivo* method, a biological sample from a treated subject is used.

Thus, the Applicants assert that Claim 1 as amended is does recite a complete method, is clear as to what the Claim is directed to, and is consistent with the method disclosed in the specification. Therefore, the Applicants submit that the rejection has been overcome and respectfully request withdrawal of the rejection with respect to Claim 1, Claims 2-12 and Claims 16-21 which depend therefrom.

Claims 22 and 23

The Examiner alleges that the elements in the Claims do not recite any structural limitations or concrete elements; rather the Examiner alleges they recite unspecified systems for performing steps in the claimed method. Addtionally, the Examiner alleges that the interrelationship between the two systems is a computational step, determination of a ratio, and not a recitation of how the two components are related.

The Applicants respectfully traverse the rejection.

Claim 22 does specify two elements: A kit comprising *a first measuring element or system* for measuring the level of at least one anti-inflammatory cytokine in a biological sample from a mammalian subject before treatment and at at least one time point after or during treatment, *a second measuring element or system* for measuring the level of at least one pro-inflammatory cytokine in a biological sample from said mammalian subject before treatment, and at at least one time point after or during treatment,…

The Examiner asserts that Claim 22 will be evaluated under 35 USC 112, 6th paragraph, and that under this section, an element maybe expressed as a means or step for performing a specified function without the recital of structure....and such claim shall be construed to cover the corresponding structure....desribed in the specification and equivalents thereof.

Therefore, the Applicants assert that structural elements need not be recited in Claim 22. Corresponding structure and measuring elements or systems are described in the specification, starting at page 11, line 27. Therefore, the Applicants assert that Claim 22 does specify two elements.

Furthermore, the Applicants submit that Claim 22 does specify the interrelationship between the two measuring elements or systems. Both measuring elements or systems measure cytokines. One system measures anti-inflammatory cytokines and the other measures pro-inflammatory cytokines. A ratio between pro- and anti-inflammatory cytokines can then be established, thus relating the two measuring elements or systems. The Applicants therefore submit that the Claim to the kit, Claim 22, does recite how the two systems are related in that both are needed in order to measure the level of a type of cytokine and the two levels are then compared in order to study the ratio between the two.

Therefore, the Applicants assert that the rejection has been overcome and respectfully request withdrawal of the rejection with respect to Claims 22 and 23.

Rejection Under 35 USC § 112, 1st Paragraph

Claims 1-12 and 16-21 are rejected under 35 USC § 112, 1st Paragraph for allegedly failing to comply with the enablement requirement.

The Examiner asserts that only methods which measure cytokine levels in tissues directly from the bowel region, or methods which measure cytokine production by peripheral blood mononuclear cells with *in vitro* stimulation, gut lymphoid tissues witn *in vitro* stimulation, or gut lymphoid tissues without *in vitro* stimulation are enabled.

Additionally, the Examiner asserts that the application is not enabled for *all* treatments, particularly treatment that involves administering anti-inflammatory cytokines or compositions which interact directly with pro-inflammatory cytokines.

The Examiner further asserts that only methods which determine changes in the ratio of the levels of IL-10/IL-12, IL-10/TNF-α, and IL-10/IFN-γ after treatment as indicative of efficacy of treatment are enabled.

The Examiner reasons that due to the allegedly large quantity of experimentation necessary to determine that changes in any cytokine level in any biological sample would be indicative of an efficacy of treatment, alleged lack of direction/guidance presented in the specification regarding same, the absence of working examples regarding same, the complex nature of the invention, the state of the art which establishes that some treatments of IBD comprise direct treatment with cytokines, and that assays of cytokine levels in some biological samples are often not meaningful, and the breadth of the claims which encompass any treatment modality and assasy utilizing any biological sample, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Additionally, the Examiner asserts that the Applicants merely invite the skilled artisan to experiment whether the measurement of cytokine levels in any given biological sample would present information useful in determining efficacy of treatment. The Examiner asserts that such invitation to experiment is not enabling.

Furthermore the Examiner asserts that administration of IL-10 or antibodies to pro-inflammatory cytokines are art-recognized methods of treating IBD. The Examiner asserts that such treatments would result in increasing IL-10 levels and/or decreasing pro-inflammatory cytokine levels which would change the ratios of levels of IL10 to IL-12 etc. but that one could not determine if such changes would be indicative of efficacy of treatment generally or are a result of the administration of therapeutic compound.

Lastly, the Examiner asserts that because the claims are drawn to methods of determining efficacy of treatment by comparing ratios of levels of anti-inflammatory to pro-inflammatory cytokines before treatment to that following treatment, one would need to determine a nexus between the cytokines and IBD, and determine which cytokine ratios are meaniful indicators of efficacy of treatment. Thus, the Examiner asserts it would require undue experimentation to determine which cytokine ratios, and changes therein, would be indicative of efficacy of treatment of inflammatory diseases of the bowel.

The Applicants respectfully traverse the rejections. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See MPEP § 2164.01 citing *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ 2d 1217, 1223 Fed. Cir. 1988. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. See MPEP § 2164.01 citing *In re Certain Limited-Charge Cell Culture Microcarriers* 221 USPQ 1165, 1174, Int'l Trade Comm'n 1983, *aff'd. sub nom., Massachusetts Institute of Technology v. A.V. Fortia,* 774 F.2d 1104, 227 USPQ 428 Fed. Cir. 1985.

As previously noted by the Examiner, the factors to be considered to determine whether experimentation is "undue" include the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a).

The Applicants assert that undue experimentation would not be required by one of skill in the art in order to practice the invention, and that the Claims, as amended, are enabled. The Applicants provide sufficient background for one of skill in the art to understand the problems associated with inflammatory bowel diseases, and the methods and technologies described in the present Specification. In addition, the level of skill of one in the art would be relatively high as the invention involves scientific and medical principles. Furthermore, complex experimentation is common to the biological and medicinal arts.

The Applicants assert that based on the description and definitions provided in the Specification, including example anti-inflammatory cytokines, pro-inflammatory cytokines, types of samples that can be tested, types of stimulating agents that can be used *in vitro* and *in vivo*, and the presence of the working example, one of skill in the art would be enabled to understand and make or use the invention.

The Applicants also assert that the Claims as amended are enabled for all of the claimed cytokines, biological samples and methods. Specific cytokines and biological samples are recited.

Additionally, the Examiner asserts that the application is not enabled for *all* treatments, particularly treatment that involves administering anti-inflammatory cytokines or compositions which interact directly with pro-inflammatory cytokines. The Applicants respectfully traverse the rejection. Even though such treatments may be known, and the subject's response might be due to the administration of an anti-inflammatory cytokine or antibody to a pro-inflammatory cytokine the methods of the Application can still be used to study the subject's response to the treatment, and to determine the effect of the treatment. Therefore, the Applicants assert that the Claims and application are enabled for all treatments.

The Examiner further asserts that only methods which determine changes in the ratio of the levels of IL-10/IL-12, IL-10/TNF-α, and IL-10/IFN-γ after treatment as indicative of efficacy of treatment are enabled. The Applicants respectfully traverse the rejection. The Claims, as amended, recite particulary anti- and pro-inflammatory cytokines. Thus, one of skill in the art would understand particular anti- and pro-inflammatory cytokines that could be used and studied. Thus, the Applicants assert that undue experimentation would not be required and the rejection has been overcome.

The Applicants therefore assert that the Claims 1-12 and 16-21, as amended, are enabled and that the rejections have been overcome. Thus, the Applicants respectfully request withdrawal of the rejections.

Rejections Under 35 USC § 102

Claim 22 is rejected under 35 USC § 102(b) as allegedly being anticipated by Vignali, 2000 Journal of Immunological Methods 243:243-255 (hereafter "Vignali").

The Examiner asserts that Claim 22, given its broadest reasonable interpretation, recites a product for measuring multiple cytokines in a biological sample from a mammalian subject. The Examiner asserts that there are no structural limitations recited as to the contents of the kit. Therefore, the Examiner asserts that ratio calculation steps do not convey patentability to the kit; that because there are no structural limitations in the Claim, a kit of the Claim could include various components of a FlowMetrix™ system as disclosed in Vignali; and that where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art.

The Applicants respectfully traverse the rejection. Under 35 USC §102, anticipation requires that all the Claim elements appear in a single prior art document. "A Claim is anticipated only if each and every element set forth in the Claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 citing *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2D 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as contained in the ... Claim." MEPE § 2131 citing *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2D 1913, 1920 (Fed. Cir. 1989).

Vignali discloses that the simultaneous detection of various analytes can be achieved using the FlowMetrix™ assay. Vignali discloses that multiple cytokine levels can be measured simultaneously. Vignali is simple a research paper that traces the historical association between microspheres and flow cytometry, the development of particle-based flow cytometric assays, how they compare with current assays and potential future developments. Vignali does not disclose a kit for measuring the particular cytokines recited in Claim 22, as amended, in a supernatant from cells cultured from a biological sample. Vignali simply discusses assay methods to measure various analytes and discusses the advantages and disadvantages of various assay methods and devices.

Therefore, because all elements of the Claim are not found in Vignali, Vignali can not, as a matter of law, anticipate the Claim. The Applicants, therefore, respectfully request that the rejection be withdrawn.

Rejections Under 35 USC § 103

Vignali

Claim 23 is rejected under 35 USC § 103(a) as being allegedly unpatentable over Vignali.

The Examiner acknowledges that Vignali does not disclose a kit comprising means for collecting biological samples. However, the Examiner asserts that it would have been obvious for one of ordinary skill in the art to include a device for obtaining a sample, that one would be motivated because it would increase the efficiency utilization of an assay to determine cytokine levels. The Examiner cites *KSR* for the assertsion that where is motivation to solve a provlem (the Examiner alleges finding means for obtainin a biological sample) and a finite number of identified, predictable solutions (the Examiner alleges for example 2 possible solutions - such means being available in a separate structure or package, or being enclosed with a kit), a person of ordinary skill has good reason to pursue the known options within his/her technical grasp.

The Applicants respectfully traverse the rejection. The Examiner has not established a *prima facie* case of obviousness, even in light of *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (U.S. 2007) ("KSR"). See also MPEP § 2143.01. KSR did not eliminate the need for at least some suggestion, motivation, or expectation of success for making a given modification. A *prima facie* case of obviousness has not been established because the cited document does not teach or suggest all of the claim limitations of Claim 23, or provide any reasonable motivation or expectation of success for trying the presently claimed invention. See MPEP § 2143.03.

The Examiner asserts that Vignali discloses a kit for measuring cytokines in a biological sample. As argued above, Vignali does not disclose a kit, nor particularly, the kit as claimed. Vignali only discloses various assay methods and devices, and compares them.

Thus, there is no suggestion, motivation or expectation to create or provide a kit. Vignali simply discusses research methods. Thus, because there is no motivation initially to create or provide a kit, there is no motivation to add to such a kit a means for collecting biological samples. Even if one of skill in the art understood that a biological sample would need to be obtained, such information would not have led one of skill in the art to the present invention. Vignali simply performs various assays on various equipment to test the limits, practicality, cost, advantages and disadvantages of various assays done on various equipment. There is nothing in Vignali that suggests a kit or provides motivation or expectation of success for creating a kit. Thus, there is no expectation of success found in Vignali for creating a kit containing a means for collecting biological samples.

Therefore, Vignali does not provide the requisite motivation, predictability or expectation of success to have led one of ordinary skill in the art to the present invention, even in light of *KSR*. Thus, the Applicants assert that the rejection has been overcome and respectfully request that the rejection be withdrawn.

Towaga

Claims 1-5, 9, 16, 17, 19, and 20 are rejected under 35 USC § 103(a) as being allegedly unpatentable over Towaga et al. 2002 Am J. Physiol, Gastrointestinal Liver Physiol 283:G187-G195 ("Towaga").

The Examiner asserts, although Towaga does not teach or suggest measuring the levels of anti and pro-inflammatory cytokines before administering a treatment, measuring cytokine levels in tissue biopsies, or determining the ratio of levels of anti- to pro-inflammatory cytokines, that it would have been obvious for one of ordinary skill to measure levels before and after treatment, that one would have been motivated to make the jump from animal model experiments to actual clinical experimentation, and that one would have been motivated to investigate and analyze ratios of levels of cytokines.

The Examiner further asserts that it would be obvious to measure cytokine levels in a biological sample before and after treatment to assess efficacy of treatment, and that one of skill in the art would be motivated to make such modifications because the Examiner

suggests that Towaga suggests clinical experimentation to determine efficacy of administration of lactoferin.

The Applicants respectfully traverse the rejection. The Examiner has made too great a leap. Towaga details a particular experiment in rats using induced colitis. Towaga does not provide any suggestion or motivation to study 'before and after' results, or to set up such experiments. Towaga does not suggest studying ratios of cytokines to establish and analyze shifts in patterns of cytokine levels to evaluate efficacy of treatment. In particular, Towaga does not suggest or provide motivation for the particular cytokines and ratios as claimed. Towaga simply induces colitis in rats and compares cytokine levels to those of normal, control rats in conjunction with studying physical aspects of the induced disease such as thickness of the colon, weight of the colon, and presence and size of lesions, in order to determine whether lactoferrin is effective against the induced colits.

There is no suggestion, motivation or predictability to do completely different clinical experiments, or to use or analyze 'before and after' data in a clinical setting simply because such things generally can be done. The Applicants assert that simply because one *could* do any variety of experiments on any compound in an animal or in a clinical setting and perform various analysis is not sufficient, even in light of *KSR*. There still must be some reason or motivation to choose a particular experiment, particular compounds to study, or particular analysis and Towaga does not provide such motivation, particularly with the wide range of possible experiments and analyses that are available to be done when studying various disease conditions.

Therefore, the disclosure of Towaga, in combination with the knowledge of one skilled in the art does not suggest the claimed invention, and one of skill in the art would not have been led to the claimed invention based on the disclosure of Towaga.

Therefore, the Applicants assert that the rejection has been overcome and respectfully request that the rejection be withdrawn.

Towaga in view of Vignali

Claims 18 and 21 are rejected under 35 USC § 103(a) as being allegedly unpatentable over Togawa as applied to Claims 1, 17 and 20 in view of Vignali. The Examiner acknowledges that Togawa does not teach a method of measuring levels of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine in a biological sample by multiplexed ELISAs using coded microspheres coupled with a flow cytometer detection system. However, The Examiner asserts that Vignali teaches a FlowMetrix™ system that uses microspheres as the solid support for a conventional immunosorbent assay. Therefore, the Examiner asserts that it would have been obvious to modify the teachings of Togawa and substitute the multiplex assay disclosed by Vignali for the ELISA assay disclosed by Togawa.

The Examiner further alleges that the Applicant has attacked the cited documents individually. The Examiner also alleges that one would anticipate success substituting the multiplex assay disclosed by Vignali for the ELISA assay disclosed by Towaga becaue both involve immunological methods of measuring cytokine concentrations. Furthermore, the Examiner asserts that knowing results of measurements of cytokine levels would provide motivation to compute ratios thereof as a way to determine shifts in patterns of cytokine levels.

The Applicants respectfully traverse the rejection. The Applicants assert that even if Towaga were combined together with Vignali and a FlowMetrix™ system were used, the claimed invention would not result. Perhaps one could analyze the cytokine levels of Towaga with such a system of Vignali. However, one would not have arrived at the claimed method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo*. Towaga and Vignali together do not suggest or provide motivation or expectation of success for a clinical method, using samples from a biological subject, in which particular cytokine levels are determined and ratios analyzed, as claimed. The Applicants therefore assert that Towaga and Vignali taken together do not contemplate such a method as claimed.

In addition, Claims 18 and 21 depend ultimately from Claim 1 which the Applicants assert is novel and non-obvious over the cited documents. Therefore, Claims 18 and 21 are also novel and non-obvious over the cited documents.

Thus, the Applicants assert that the rejection has been overcome and respectfully request that the rejection be withdrawn.

Towaga in view of Blumberg

Claims 6-8 are rejected under 35 USC § 103(a) as being allegedly unpatentable over Togawa as applied to Claim 1 in view of Blumberg et al. 1999 Current Opinion in Immunology 11:648-656 ("Blumberg"). The Examiner acknowledges that Togawa does not disclose the particular claimed ratios of cytokines. However, the Examiner asserts that Togawa teaches measurement of various cytokines, and that Blumberg teaches the importance of the balance of cytokines in IBD pathogenesis. Therefore, the Examiner asserts that it would have been obvious to modify the teachings of Togawa and substitute measurement of pro-inflammatory cytokines as taught by Blumberg. The Examiner also asserts that calculation of ratios would have been obvious as a way of monitoring changes in the balance of levels of pro- and anti-inflammatory cytokines.

Additionally, the Examiner asserts that both Towaga and Blumberg disclose the importance of disturbed balance between pro- and anti-inflammatory cytokines in inflammatory bowel disease. The Examiner also asserts that one would be motivated to measure changes in cytokine levels because Towaga discloses changes in cytokine levels in response to administration of lactoferrin.

The Applicants respectfully traverse the rejection. As argued above, Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios. Blumberg also does not suggest establishing or analyzing ratios of cytokines, nor importance of . Blumberg simply notes that there is likely an on-going balance between pro- and anti-inflammatory cytokines, and their release and activity in body systems in relation to inflammation. Blumberg is simply a review of known animal models of mucosal inflammation and their *potential* relation to human inflammatory bowel disease.

Blumberg summarizes which animal models might be better for studying various types of inflammatory bowel disease such as Ulcerative Colitis and Crohn's Disease. Blumberg does not suggest or provide motivation, expectation of success or predictability for particular methods of evaluating efficacy of treatments. Therefore, the Applicants assert that even if one were to have combined the disclosure of Towaga and Blumberg, one would not have arrived at the Applicants' invention, as claimed.

In addition, Claims 6-8 depend from Claim 1 which the Applicants assert is novel and non-obvious over the cited documents. Therefore, Claims 6-8 are also novel and non-obvious over the cited documents.

Thus, the Applicants assert that the rejection has been overcome and respectfully request withdrawal of the rejection.

Conclusion

This response represents an earnest effort to place the application in proper form and to distinguish the invention as now claimed from the applied documents. In view of the foregoing, reconsideration of this application, entry of the amendments presented herein, withdrawal of the rejections, and allowance of all pending Claims is respectfully requested. Early and favorable action in the case is respectfully requested. If the Examiner desires to speak with the Applicants' attorney, the Examiner is invited to please contact the undersigned.

Respectfully submitted,

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